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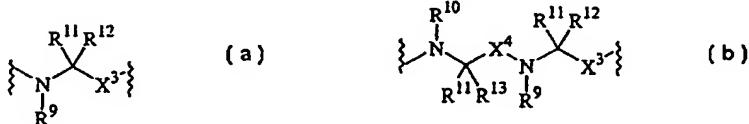
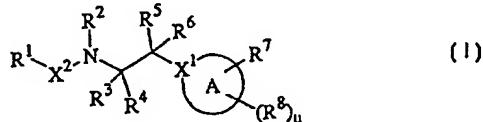
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(54) Title: AMINE DERIVATIVES AS PROTEASE INHIBITORS



(57) Abstract

The present invention relates to novel alkanoyl-substituted heterocyclic derivatives which are cysteine protease inhibitors; the pharmaceutically acceptable salts and *N*-oxides thereof; their uses as therapeutic agents and the methods of their making; according to Formula (1) in which: A comprises a heteromonocyclic ring containing 5 to 6 ring member atoms or a fused heteropolycyclic ring system containing 8 to 14 ring member atoms, wherein each ring contains 5 to 7 ring member atoms, X¹ is a ring member carbon atom and each ring member atom other than X¹ is a carbon atom or a heteroatom, with the proviso that (i) at least one ring member atom is a heteroatom and (ii) when A is a heteromonocyclic radical containing 5 ring member atoms, no more than two of the ring member atoms comprising A are heteroatoms; n is 0, 1, 2 or 3; X¹ is =C- or -CH-; X² is a bond or a divalent group of Formula (a) or (b); R¹ - R⁸ = as in the application.

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AMINE DERIVATIVES AS PROTEASE INHIBITORS

THE INVENTION

This application relates to compounds and compositions for treating diseases associated
5 with cysteine protease activity, particularly diseases associated with activity of cathepsins B, K,
L or S.

DESCRIPTION OF THE FIELD

Cysteine proteases represent a class of peptidases characterized by the presence of a cysteine residue in the catalytic site of the enzyme. Cysteine proteases are associated with the
10 normal degradation and processing of proteins. The aberrant activity of cysteine proteases, e.g. as a result of increased expression or enhanced activation, however, may have pathological consequences. In this regard, certain cysteine proteases are associated with a number of disease states, including arthritis, muscular dystrophy, inflammation, tumor invasion, glomerulonephritis, malaria, periodontal disease, metachromatic leukodystrophy and others. For
15 example, increased cathepsin B levels and redistribution of the enzyme are found in tumors; thus, suggesting a role for the enzyme in tumor invasion and metastasis. In addition, aberrant cathepsin B activity is implicated in such disease states as rheumatoid arthritis, osteo arthritis, pneumocystis carinii, acute pancreatitis, inflammatory airway disease and bone and joint disorders.

20 The prominent expression of cathepsin K in osteoclasts and osteoclast-related multinucleated cells and its high collagenolytic activity suggest that the enzyme is involved in ososteoclast-mediated bone resorption and, hence, in bone abnormalities such as occurs in osteoporosis. In addition, cathepsin K expression in the lung and its elastinolytic activity suggest that the enzyme plays a role in pulmonary disorders as well.

25 Cathepsin L is implicated in normal lysosomal proteolysis as well as several disease states, including, but not limited to, metastasis of melanomas. Cathepsin S is implicated in Alzheimer's disease and certain autoimmune disorders, including, but not limited to juvenile onset diabetes, multiple sclerosis, pemphigus vulgaris, Graves' disease, myasthenia gravis, systemic lupus erythematosus, rheumatoid arthritis and Hashimoto's thyroiditis; allergic

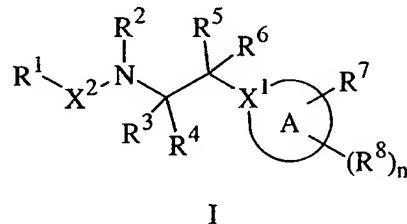
disorders, including, but not limited to asthma; and allogeneic immune responses, including, but not limited to, rejection of organ transplants or tissue grafts.

In view of the number of diseases wherein it is recognized that an increase in cysteine protease activity contributes to the pathology and/or symptomatology of the disease, molecules 5 which are shown to inhibit the activity of this class of enzymes, in particular molecules which are inhibitors of cathepsins B, K, L and/or S, will be useful as therapeutic agents.

SUMMARY OF THE INVENTION

In one particular embodiment, the present invention relates to protease inhibitors of Formula I:

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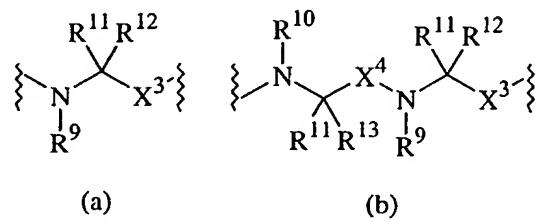
in which:

A comprises a heteromonocyclic ring containing 5 to 6 ring member atoms or a fused heteropolycyclic ring system containing 8 to 14 ring member atoms, wherein each ring contains 5 to 7 ring member atoms, X¹ is a ring member carbon atom and each ring member atom other 15 than X¹ is a carbon atom or a heteroatom, with the proviso that (i) at least one ring member atom is a heteroatom and (ii) when A is a heteromonocyclic radical containing 5 ring member atoms, no more than two of the ring member atoms comprising A are heteroatoms;

n is 0, 1, 2 or 3;

X¹ is =C- or -CH-;

20 X² is a bond or a divalent group of Formula (a) or (b):



wherein:

X^3 and X^4 independently are $-C(O)-$ or $-CH_2S(O)_2-$
 R^9 and R^{10} independently are hydrogen, (C_{1-6}) alkyl or as defined below;
 R^{11} at each occurrence independently is hydrogen or (C_{1-6}) alkyl;
 R^{12} and R^{13} independently are (i) (C_{1-6}) alkyl optionally substituted with cyano,
5 halo, nitro, $-NR^{14}R^{14}$, $-NR^{14}C(O)OR^{14}$, $-NR^{14}C(O)NR^{14}R^{14}$, $-NR^{14}C(NR^{14})NR^{14}R^{14}$,
 $-OR^{14}$, $-SR^{14}$, $-C(O)OR^{14}$, $-C(O)NR^{14}R^{14}$, $-S(O)_2NR^{14}R^{14}$, $-P(O)(OR^{14})OR^{14}$,
 $-OP(O)(OR^{14})OR^{14}$, $-NR^{14}C(O)R^{15}$, $-S(O)R^{15}$, $-S(O)_2R^{15}$, $-C(O)R^{15}$, $-OR^{16}$, $-SR^{16}$,
 $-S(O)R^{16}$, $-S(O)_2R^{16}$, $-C(O)R^{16}$, $-C(O)OR^{16}$, $-OC(O)R^{16}$, $-NR^{16}R^{17}$, $-NR^{17}C(O)R^{16}$,
 $-NR^{17}C(O)OR^{16}$, $-C(O)NR^{16}R^{17}$, $-S(O)_2NR^{16}R^{17}$, $-NR^{17}C(O)NR^{16}R^{17}$ or
10 $-NR^{17}C(NR^{17})NR^{16}R^{17}$, wherein R^{14} at each occurrence independently is hydrogen,
 (C_{1-6}) alkyl or halo-substituted (C_{1-3}) alkyl, R^{15} is (C_{1-6}) alkyl or halo-substituted
 (C_{1-3}) alkyl, halo, (C_{1-6}) alkyl or R^{16} is (C_{3-12}) cycloalkyl(C_{0-6})alkyl,
 hetero(C_{3-12})cycloalkyl(C_{0-6})alkyl, (C_{6-12}) aryl(C_{0-6})alkyl, hetero(C_{5-12})aryl(C_{0-6})alkyl,
 (C_{9-12}) polycycloaryl(C_{0-6})alkyl or hetero(C_{8-12})polycycloaryl(C_{0-6})alkyl and R^{17} is
15 hydrogen or (C_{1-6}) alkyl, and wherein within R^{16} said cycloalkyl, heterocycloalkyl, aryl,
 heteroaryl, polycycloaryl or heteropolycycloaryl ring optionally is substituted by a group
 selected from $-R^{18}$, $-X^5OR^{18}$, $-X^5SR^{18}$, $-X^5S(O)R^{18}$, $-X^5S(O)_2R^{18}$, $-X^5C(O)R^{18}$,
 $-X^5C(O)OR^{18}$, $-X^5OC(O)R^{18}$, $-X^5NR^{18}R^{19}$, $-X^5NR^{19}C(O)R^{18}$, $-X^5NR^{19}C(O)OR^{18}$,
 $-X^5C(O)NR^{18}R^{19}$, $-X^5S(O)_2NR^{18}R^{19}$, $-X^5NR^{19}C(O)NR^{18}R^{19}$ or
20 $-X^5NR^{19}C(NR^{19})NR^{18}R^{19}$, wherein X^5 is a bond or (C_{1-6}) alkylene, R^{18} is hydrogen or
 (C_{1-6}) alkyl and R^{19} is (C_{3-12}) cycloalkyl(C_{0-6})alkyl, hetero(C_{3-12})cycloalkyl(C_{0-6})alkyl,
 (C_{6-12}) aryl(C_{0-6})alkyl, hetero(C_{5-12})aryl(C_{0-6})alkyl, (C_{9-12}) polycycloaryl(C_{0-6})alkyl or
 hetero(C_{8-12})polycycloaryl(C_{0-6})alkyl, or (ii) a group selected from
 (C_{3-12}) cycloalkyl(C_{0-6})alkyl, hetero(C_{3-12})cycloalkyl(C_{0-6})alkyl, (C_{6-12}) aryl(C_{0-6})alkyl,
25 hetero(C_{5-12})aryl(C_{0-6})alkyl, (C_{9-12}) polycycloaryl(C_{0-6})alkyl and
 hetero(C_{8-12})polycycloaryl(C_{0-6})alkyl, wherein said cycloalkyl, heterocycloalkyl, aryl,
 heteroaryl, polycycloaryl or heteropolycycloaryl ring optionally is substituted by a group
 selected from $-R^{18}$, $-X^5OR^{18}$, $-X^5SR^{18}$, $-X^5S(O)R^{18}$, $-X^5S(O)_2R^{18}$, $-X^5C(O)R^{18}$,
 $-X^5C(O)OR^{18}$, $-X^5OC(O)R^{18}$, $-X^5NR^{18}R^{19}$, $-X^5NR^{19}C(O)R^{18}$, $-X^5NR^{19}C(O)OR^{18}$,
30 $-X^5C(O)NR^{18}R^{19}$, $-X^5S(O)_2NR^{18}R^{19}$, $-X^5NR^{19}C(O)NR^{18}R^{19}$ or
 $-X^5NR^{19}C(NR^{19})NR^{18}R^{19}$, wherein X^5 , R^{18} and R^{19} are as defined above; wherein
 within R^{12} and/or R^{13} any alicyclic or aromatic ring system present may be substituted

further by 1 to 5 radicals independently selected from (C₁₋₆)alkyl, (C₁₋₆)alkylidene, cyano, halo, halo-substituted (C₁₋₄)alkyl, nitro, -X⁵NR¹⁴R¹⁴, -X⁵NR¹⁴C(O)OR¹⁴, -X⁵NR¹⁴C(O)NR¹⁴R¹⁴, -X⁵NR¹⁴C(NR¹⁴)NR¹⁴R¹⁴, -X⁵OR¹⁴, -X⁵SR¹⁴, -X⁵C(O)OR¹⁴, -X⁵C(O)NR¹⁴R¹⁴, -X⁵S(O)₂NR¹⁴R¹⁴, -X⁵P(O)(OR¹⁴)OR¹⁴, -X⁵OP(O)(OR¹⁴)OR¹⁴, -X⁵NR¹⁴C(O)R¹⁵, -X⁵S(O)R¹⁵, -X⁵S(O)₂R¹⁵ and -X⁵C(O)R¹⁵, wherein X⁵, R¹⁴ and R¹⁵ are as defined above; or

5 R¹² together with R⁹ and/or R¹³ together with R¹⁰ form trimethylene, tetramethylene or phenylene-1,2-dimethylene, optionally substituted with 1 to 3 radicals independently selected from (C₁₋₆)alkyl, (C₁₋₆)alkylidene, cyano, halo, halo-substituted (C₁₋₄)alkyl, nitro, oxo, -X⁵NR¹⁴C(O)OR¹⁴, -X⁵NR¹⁴C(O)NR¹⁴R¹⁴, -X⁵NR¹⁴C(NR¹⁴)NR¹⁴R¹⁴, -X⁵OR¹⁴, -X⁵SR¹⁴, -X⁵C(O)OR¹⁴, -X⁵C(O)NR¹⁴R¹⁴, -X⁵S(O)₂NR¹⁴R¹⁴, -X⁵P(O)(OR¹⁴)OR¹⁴, -X⁵OP(O)(OR¹⁴)OR¹⁴, -X⁵NR¹⁴C(O)R¹⁵, -X⁵S(O)R¹⁵, -X⁵S(O)₂R¹⁵ and -X⁵C(O)R¹⁵, wherein X⁵, R¹⁴ and R¹⁵ are as defined above; and

10 15 R¹ is -X⁶X⁷R²⁰, wherein X⁶ is -C(O)-, -C(O)C(O)- or -S(O)₂-, X⁷ is a bond, -O- or -NR²¹-, wherein R²¹ is hydrogen or (C₁₋₆)alkyl, and R²⁰ is (i) (C₁₋₆)alkyl optionally substituted by cyano, halo, nitro, -NR¹⁴R¹⁴, -NR¹⁴C(O)OR¹⁴, -NR¹⁴C(O)NR¹⁴R¹⁴, -NR¹⁴C(NR¹⁴)NR¹⁴R¹⁴, -OR¹⁴, -SR¹⁴, -C(O)OR¹⁴, -C(O)NR¹⁴R¹⁴, -S(O)₂NR¹⁴R¹⁴, -P(O)(OR¹⁴)OR¹⁴, -OP(O)(OR¹⁴)OR¹⁴, -NR¹⁴C(O)R¹⁵, -S(O)R¹⁵, -S(O)₂R¹⁵, -C(O)R¹⁵, -OR²², -SR²², -S(O)R²², -S(O)₂R²², -C(O)R²², -C(O)OR²², -C(O)NR²²R²³, -NR²²R²³, -NR²³C(O)R²², -NR²³C(O)OR²², -NR²³C(O)NR²²R²³ or -NR²³C(NR²³)NR²²R²³, wherein R¹⁴ and R¹⁵ are as defined above, R²² is (C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl, hetero(C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl, (C₆₋₁₂)aryl(C₀₋₆)alkyl, hetero(C₅₋₁₂)aryl(C₀₋₆)alkyl, (C₉₋₁₂)bicycloaryl(C₀₋₆)alkyl or hetero(C₈₋₁₂)bicycloaryl(C₀₋₆)alkyl and R²³ at each occurrence independently is hydrogen or (C₁₋₆)alkyl, or

20 25 (ii) (C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl, hetero(C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl, (C₆₋₁₂)aryl(C₀₋₆)alkyl, hetero(C₅₋₁₂)aryl(C₀₋₆)alkyl, (C₉₋₁₂)bicycloaryl(C₀₋₆)alkyl or hetero(C₈₋₁₂)bicycloaryl(C₀₋₆)alkyl or (iii) (C₃₋₆)cycloalkyl(C₀₋₆)alkyl, hetero(C₃₋₆)cycloalkyl(C₀₋₆)alkyl, phenyl(C₀₋₆)alkyl or hetero(C₅₋₆)aryl(C₀₋₆)alkyl, wherein said cycloalkyl, heterocycloalkyl, phenyl or heteroaryl is substituted by -R²⁴, -X⁵OR²⁴, -X⁵SR²⁴, -X⁵S(O)R²⁴, -X⁵S(O)₂R²⁴, -X⁵C(O)R²⁴, -X⁵C(O)OR²⁴, -X⁵C(O)NR²⁴R²⁵, -X⁵NR²⁴R²⁵, -X⁵NR²⁴C(O)R²⁴, -X⁵NR²⁵C(O)OR²⁴, -X⁵NR²⁵C(O)NR²⁴R²⁵ or -X⁵NR²⁵C(NR²⁵)NR²⁴R²⁵, wherein X⁵ is as defined above, R²⁴ is (C₃₋₆)cycloalkyl(C₀₋₆)alkyl, hetero(C₃₋₆)cycloalkyl(C₀₋₆)alkyl, phenyl(C₀₋₆)alkyl or hetero(C₅₋₆)aryl(C₀₋₆)alkyl and R²⁵ at each

occurrence independently is hydrogen or $(C_{1-6})alkyl$; wherein within R^1 any alicyclic or aromatic ring system present may be substituted further by 1 to 5 radicals independently selected from $(C_{1-6})alkyl$, $(C_{1-6})alkylidene$, cyano, halo, halo-substituted $(C_{1-4})alkyl$, nitro, $-X^5NR^{14}R^{14}$, $-X^5NR^{14}C(O)OR^{14}$, $-X^5NR^{14}C(O)NR^{14}R^{14}$, $-X^5NR^{14}C(NR^{14})NR^{14}R^{14}$, $-X^5OR^{14}$, $-X^5SR^{14}$, $-X^5C(O)OR^{14}$, $-X^5C(O)NR^{14}R^{14}$, $-X^5S(O)_2NR^{14}R^{14}$, $-X^5P(O)(OR^{14})OR^{14}$, $-X^5OP(O)(OR^{14})OR^{14}$, $-X^5NR^{14}C(O)R^{15}$, $-X^5S(O)R^{15}$, $-X^5S(O)_2R^{15}$ and $-X^5C(O)R^{15}$, wherein X^5 , R^{14} and R^{15} are as defined above; or when X^2 is a divalent group of formula (a) or (b) then R^1 may also represent hydrogen, carboxy, oxalo or carbamoyl;

R^2 is hydrogen or $(C_{1-6})alkyl$;

10 R^3 is (i) $(C_{1-6})alkyl$ optionally substituted with cyano, halo, nitro, $-SR^{26}$, $-C(O)OR^{26}$, $-C(O)NR^{26}R^{26}$, $-P(O)(OR^{26})OR^{26}$, $-OP(O)(OR^{26})OR^{26}$, $-S(O)R^{27}$, $-S(O)_2R^{27}$ or $-C(O)R^{27}$, wherein R^{26} at each occurrence independently is hydrogen, $(C_{1-6})alkyl$ or halo-substituted $(C_{1-3})alkyl$ and R^{27} is $(C_{1-6})alkyl$ or halo-substituted $(C_{1-3})alkyl$, or (ii) $(C_{5-6})cycloalkyl(C_{2-3})alkyl$, hetero $(C_{3-6})cycloalkyl(C_{2-3})alkyl$, $(C_{6-12})aryl(C_{2-3})alkyl$ or hetero $(C_{5-6})aryl(C_{2-3})alkyl$, wherein 15 said cycloalkyl, heterocycloalkyl, aryl or heteroaryl optionally is substituted further with 1 to 5 radicals independently selected from $(C_{1-6})alkyl$, $(C_{1-6})alkylidene$, cyano, halo, halo-substituted $(C_{1-4})alkyl$, nitro, $-X^5NR^{14}C(O)OR^{14}$, $-X^5NR^{14}C(O)NR^{14}R^{14}$, $-X^5NR^{14}C(NR^{14})NR^{14}R^{14}$, $-X^5OR^{14}$, $-X^5SR^{14}$, $-X^5C(O)OR^{14}$, $-X^5C(O)NR^{14}R^{14}$, $-X^5S(O)_2NR^{14}R^{14}$, $-X^5P(O)(OR^{14})OR^{14}$, $-X^5OP(O)(OR^{14})OR^{14}$, $-X^5NR^{14}C(O)R^{15}$, $-X^5S(O)R^{15}$, $-X^5S(O)_2R^{15}$ and $-X^5C(O)R^{15}$, wherein 20 X^5 , R^{14} and R^{15} are as defined above, provided that when R^3 is unsubstituted $(C_{1-5})alkyl$ and R^4 is hydrogen or unsubstituted $(C_{1-5})alkyl$, then X^2 may not represent (i) a bond when R^1 is $-C(O)R^{20}$, $-C(O)_2R^{20}$ or $-S(O)_2R^{20}$ in which R^{20} is $(C_{1-6})alkyl$, phenyl $(C_{1-4})alkyl$, phenyl, $(C_{3-7})cycloalkyl$, camphan-10-yl, naphth-1-yl, naphth-2-yl, phenyl substituted by one or more of $(C_{1-4})alkyl$, perfluoro $(C_{1-4})alkyl$, $(C_{1-4})alkoxy$, hydroxy, halo, amido, nitro, amino, 25 $(C_{1-4})alkylamino$, $(C_{1-4})dialkylamino$, carboxy or $(C_{1-4})alkoxycarbonyl$, or naphth-1-yl or naphth-2-yl substituted by one or more of $(C_{1-4})alkyl$, perfluoro $(C_{1-4})alkyl$, $(C_{1-4})alkoxy$, hydroxy, halo, amido, nitro, amino, carboxy or $(C_{1-4})alkoxycarbonyl$ or (ii) a divalent group of formula (a) or (b) in which the moiety R^{12} is methyl, isopropyl, *n*-butyl, *sec*-butyl, *tert*-butyl, 1-methylpropyl, benzyl, naphth-1-ylmethyl, naphth-2-ylmethyl, thien-2-ylmethyl, thien-3-ylmethyl, or wherein R^9 30 and R^{12} form ethylene, trimethylene, hydroxy-substituted trimethylene, tetramethylene or phenylene-1,2-dimethylene; or

R^3 and R^4 taken together with the carbon atom to which both R^3 and R^4 are attached

form (C_{3-8}) cycloalkylene or (C_{3-8}) heterocycloalkylene, wherein said cycloalkylene or heterocycloalkylene is optionally substituted with 1 to 3 radicals independently selected from (C_{1-6}) alkyl, (C_{1-6}) alkylidene, cyano, halo, halo-substituted (C_{1-4}) alkyl, nitro, $-X^5NR^{14}C(O)OR^{14}$, $-X^5NR^{14}C(O)NR^{14}R^{14}$, $-X^5NR^{14}C(NR^{14})NR^{14}R^{14}$, $-X^5OR^{14}$, $-X^5SR^{14}$, $-X^5C(O)OR^{14}$, $5 -X^5C(O)NR^{14}R^{14}$, $-X^5S(O)_2NR^{14}R^{14}$, $-X^5P(O)(OR^{14})OR^{14}$, $-X^5OP(O)(OR^{14})OR^{14}$, $-X^5NR^{14}C(O)R^{15}$, $-X^5S(O)R^{15}$, $-X^5S(O)_2R^{15}$ and $-X^5C(O)R^{15}$, wherein X^5 , R^{14} and R^{15} are as defined above;

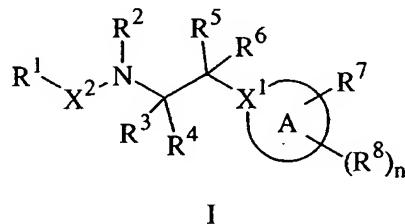
R^4 is hydrogen, (C_{1-6}) alkyl or as defined above;

R^5 is hydrogen and R^6 is hydroxy or R^5 and R^6 together form oxo;

10 R^7 is a group selected from cyano, halo, nitro, $-R^{29}$, $-X^5NR^{29}R^{30}$, $-X^5NR^{30}C(O)OR^{29}$, $-X^5NR^{30}C(O)NR^{29}R^{30}$, $-X^5NR^{30}C(NR^{30})NR^{29}R^{30}$, $-X^5OR^{29}$, $-X^5SR^{29}$, $-X^5C(O)OR^{29}$, $-X^5C(O)NR^{29}R^{30}$, $-X^5S(O)_2NR^{29}R^{30}$, $-X^5P(O)(OR^{30})OR^{29}$, $-X^5OP(O)(OR^{29})OR^{29}$, $-X^5NR^{30}C(O)R^{31}$, $-X^5S(O)R^{31}$, $-X^5S(O)_2R^{31}$ and $-X^5C(O)R^{31}$, wherein X^5 is as defined above, R^{29} is hydrogen or $-R^{31}$, R^{30} at each occurrence is hydrogen or (C_{1-6}) alkyl and R^{31} is (C_{1-6}) alkyl, $15 (C_{3-12})$ cycloalkyl(C_{0-6})alkyl, hetero(C_{3-12})cycloalkyl(C_{0-6})alkyl, (C_{6-12}) aryl(C_{0-6})alkyl or hetero(C_{5-12})aryl(C_{0-6})alkyl, wherein within R^7 any alicyclic or aromatic ring system present may be substituted further by 1 to 5 radicals independently selected from (C_{1-6}) alkyl, (C_{1-6}) alkylidene, cyano, halo, halo-substituted (C_{1-4}) alkyl, nitro, $-X^5NR^{14}R^{14}$, $-X^5NR^{14}C(O)OR^{14}$, $-X^5NR^{14}C(O)NR^{14}R^{14}$, $-X^5NR^{14}C(NR^{14})NR^{14}R^{14}$, $-X^5OR^{14}$, $-X^5SR^{14}$, $-X^5C(O)OR^{14}$, $20 -X^5C(O)NR^{14}R^{14}$, $-X^5S(O)_2NR^{14}R^{14}$, $-X^5P(O)(OR^{14})OR^{14}$, $-X^5OP(O)(OR^{14})OR^{14}$, $-X^5NR^{14}C(O)R^{15}$, $-X^5S(O)R^{15}$, $-X^5S(O)_2R^{15}$ and $-X^5C(O)R^{15}$, wherein X^5 , R^{14} and R^{15} are as defined above; and

R^8 at each occurrence independently is selected from (C_{1-6}) alkyl, (C_{1-6}) alkylidene, cyano, halo, halo-substituted (C_{1-4}) alkyl, nitro, $-X^5NR^{14}R^{14}$, $-X^5NR^{14}C(O)OR^{14}$, $25 -X^5NR^{14}C(O)NR^{14}R^{14}$, $-X^5NR^{14}C(NR^{14})NR^{14}R^{14}$, $-X^5OR^{14}$, $-X^5SR^{14}$, $-X^5C(O)OR^{14}$, $-X^5C(O)NR^{14}R^{14}$, $-X^5S(O)_2NR^{14}R^{14}$, $-X^5P(O)(OR^{14})OR^{14}$, $-X^5OP(O)(OR^{14})OR^{14}$, $-X^5NR^{14}C(O)R^{15}$, $-X^5S(O)R^{15}$, $-X^5S(O)_2R^{15}$ and $-X^5C(O)R^{15}$, wherein X^5 , R^{14} and R^{15} are as defined above; and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers; and the pharmaceutically acceptable salts thereof.; but 30 excluding compounds selected from the group consisting of $((S)-1-[(S)-1-[(S)-1-(1-benzoazol-2-yl-methanoyl)-3-methyl-butylcarbamoyl]-3-methyl-butylcarbamoyl]-3-methyl-butyl)-carbamic acid benzyl ester, \{1-[1-(1-1H-imidazol-2-yl-$

methanoyl)-3-methyl-butylcarbamoyl]-3-methyl-butyl)-carbamic acid *tert*-butyl ester,
 [(S)-3-methyl-1-((S)-3-methyl-1-{1-[1-(2-trimethylsilyl-ethoxymethyl)-1*H*-imidazol-2-yl]-
 methanoyl}-butylcarbamoyl)-butyl]-carbamic acid benzyl ester;
 {((S)-1-[(S)-1-(1*H*-imidazol-2-yl-methanoyl)-3-methyl-butylcarbamoyl]-3-methyl-butyl)-
 5 carbamic acid benzyl ester, ((S)-1-((S)-1-1-(1-benzyl-1*H*-imidazol-2-yl)-methanoyl]-3-methyl-
 butylcarbamoyl)-3-methyl-butyl)-carbamic acid benzyl ester, {((S)-1-[(S)-1-(1*H*-imidazol-2-yl-
 methanoyl)-3-methyl-butylcarbamoyl]-3-methyl-butyl)-carbamic acid *tert*-butyl ester,
 3-{{1-(4-chloro-phenyl)-methanoyl]-amino}-4-oxo-4-pyridin-3-yl-butyric acid ethyl ester,
 4-furan-2-yl-4-oxo-3-{{1-(4-trifluoromethyl-phenyl)-methanoyl]-amino}-butyric acid ethyl ester,
 10 3-(2-methyl-propanoylamino)-4-oxo-4-thiophen-2-yl-butyric acid ethyl ester, 4-oxo-
 4-thiophen-2-yl-3-{{(1-*p*-tolyl-methanoyl)-amino}-butyric acid ethyl ester, 4-(5-bromo-
 thiophen-2-yl)-3-{{1-(4-chloro-phenyl)-methanoyl]-amino}-4-oxo-butyric acid ethyl ester,
 3-{{1-(4-chloro-phenyl)-methanoyl]-amino}-4-(5-methyl-thiophen-2-yl)-4-oxo-butyric acid ethyl
 ester, 4-oxo-4-thiophen-3-yl-3-{{(1-*p*-tolyl-methanoyl)-amino}-butyric acid ethyl ester,
 15 3-{{1-(4-methoxy-phenyl)-methanoyl]-amino}-4-oxo-4-thiophen-3-yl-butyric acid ethyl ester,
 3-{{1-(3,4-dichloro-phenyl)-methanoyl]-amino}-4-oxo-4-thiophen-3-yl-butyric acid ethyl ester,
 4-fluoro-*N*-{{1-(1-thiophen-3-yl-methanoyl)-propyl}-benzamide, 4-{{1-(4-fluoro-phenyl)-
 methanoyl]-amino}-5-oxo-5-thiophen-3-yl-pentanoic acid ethyl ester and 3-{{1-(4-fluoro-
 phenyl)-methanoyl]-amino}-2-methyl-4-oxo-4-thiophen-3-yl-butyric acid ethyl ester.
 20 In another particular embodiment, the present invention relates to protease inhibitors of
 Formula I:



in which:

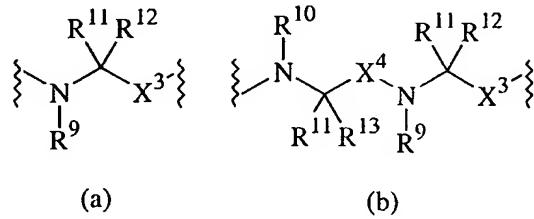
A comprises a heteromonocyclic ring containing 5 to 6 ring member atoms or a fused
 25 heteropolycyclic ring system containing 8 to 14 ring member atoms, wherein each ring contains
 5 to 7 ring member atoms, X¹ is a ring member carbon atom and each ring member atom other
 than X¹ is a carbon atom or a heteroatom, with the proviso that (i) at least one ring member

atom is a heteroatom and (ii) when A is a heteromonocyclic radical containing 5 ring member atoms, no more than two of the ring member atoms comprising A are heteroatoms;

n is 0, 1, 2 or 3;

X¹ is =C- or -CH-;

5 X² is a bond or a divalent group of Formula (a) or (b):



wherein:

X³ and X⁴ independently are -C(O)- or -CH₂S(O)₂-;

R⁹ and R¹⁰ independently are hydrogen, (C₁₋₆)alkyl or as defined below;

10 R¹¹ at each occurrence independently is hydrogen or (C₁₋₆)alkyl;

R¹² and R¹³ independently are (i) (C₁₋₆)alkyl optionally substituted with cyano, halo, nitro, -NR¹⁴R¹⁴, -NR¹⁴C(O)OR¹⁴, -NR¹⁴C(O)NR¹⁴R¹⁴, -NR¹⁴C(NR¹⁴)NR¹⁴R¹⁴, -OR¹⁴, -SR¹⁴, -C(O)OR¹⁴, -C(O)NR¹⁴R¹⁴, -S(O)₂NR¹⁴R¹⁴, -P(O)(OR¹⁴)OR¹⁴,

-OP(O)(OR¹⁴)OR¹⁴, -NR¹⁴C(O)R¹⁵, -S(O)R¹⁵, -S(O)₂R¹⁵, -C(O)R¹⁵, -OR¹⁶, -SR¹⁶,

-S(O)R¹⁶, -S(O)₂R¹⁶, -C(O)R¹⁶, -C(O)OR¹⁶, -OC(O)R¹⁶, -NR¹⁶R¹⁷, -NR¹⁷C(O)R¹⁶,

-NR¹⁷C(O)OR¹⁶, -C(O)NR¹⁶R¹⁷, -S(O)₂NR¹⁶R¹⁷, -NR¹⁷C(O)NR¹⁶R¹⁷ or

-NR¹⁷C(NR¹⁷)NR¹⁶R¹⁷, wherein R¹⁴ at each occurrence independently is hydrogen,

(C₁₋₆)alkyl or halo-substituted (C₁₋₃)alkyl, R¹⁵ (C₁₋₆)alkyl or halo-substituted (C₁₋₃)alkyl, R¹⁶ is (C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl, hetero(C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl,

20 (C₆₋₁₂)aryl(C₀₋₆)alkyl, hetero(C₅₋₁₂)aryl(C₀₋₆)alkyl, (C₉₋₁₂)polycycloaryl(C₀₋₆)alkyl or

hetero(C₈₋₁₂)polycycloaryl(C₀₋₆)alkyl and R¹⁷ is hydrogen or (C₁₋₆)alkyl, and wherein within R¹⁶ said cycloalkyl, heterocycloalkyl, aryl, heteroaryl, polycycloaryl or

heteropolycycloaryl ring optionally is substituted by a group selected from -R¹⁸, -X⁵OR¹⁸,

-X⁵SR¹⁸, -X⁵S(O)R¹⁸, -X⁵S(O)₂R¹⁸, -X⁵C(O)R¹⁸, -X⁵C(O)OR¹⁸, -X⁵OC(O)R¹⁸,

25 -X⁵NR¹⁸R¹⁹, -X⁵NR¹⁹C(O)R¹⁸, -X⁵NR¹⁹C(O)OR¹⁸, -X⁵C(O)NR¹⁸R¹⁹,

-X⁵S(O)₂NR¹⁸R¹⁹, -X⁵NR¹⁹C(O)NR¹⁸R¹⁹ or -X⁵NR¹⁹C(NR¹⁹)NR¹⁸R¹⁹, wherein X⁵ is a

bond or (C₁₋₆)alkylene, R¹⁸ is hydrogen or (C₁₋₆)alkyl and R¹⁹ is

(C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl, hetero(C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl, (C₆₋₁₂)aryl(C₀₋₆)alkyl, hetero(C₅₋₁₂)aryl(C₀₋₆)alkyl, (C₉₋₁₂)polycycloaryl(C₀₋₆)alkyl or hetero(C₈₋₁₂)polycycloaryl(C₀₋₆)alkyl, or (ii) a group selected from (C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl, hetero(C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl, (C₆₋₁₂)aryl(C₀₋₆)alkyl, 5 hetero(C₅₋₁₂)aryl(C₀₋₆)alkyl, (C₉₋₁₂)polycycloaryl(C₀₋₆)alkyl and hetero(C₈₋₁₂)polycycloaryl(C₀₋₆)alkyl, wherein said cycloalkyl, heterocycloalkyl, aryl, heteroaryl, polycycloaryl or heteropolycycloaryl ring optionally is substituted by a group selected from -R¹⁸, -X⁵OR¹⁸, -X⁵SR¹⁸, -X⁵S(O)R¹⁸, -X⁵S(O)₂R¹⁸, -X⁵C(O)R¹⁸, -X⁵C(O)OR¹⁸, -X⁵OC(O)R¹⁸, -X⁵NR¹⁸R¹⁹, -X⁵NR¹⁹C(O)R¹⁸, -X⁵NR¹⁹C(O)OR¹⁸, -X⁵C(O)NR¹⁸R¹⁹, -X⁵S(O)₂NR¹⁸R¹⁹, -X⁵NR¹⁹C(O)NR¹⁸R¹⁹ or -X⁵NR¹⁹C(NR¹⁹)NR¹⁸R¹⁹, wherein X⁵, R¹⁸ and R¹⁹ are as defined above; wherein 10 within R¹² and/or R¹³ any alicyclic or aromatic ring system present may be substituted further by 1 to 5 radicals independently selected from (C₁₋₆)alkyl, (C₁₋₆)alkylidene, cyano, halo, halo-substituted (C₁₋₄)alkyl, nitro, -X⁵NR¹⁴R¹⁴, -X⁵NR¹⁴C(O)OR¹⁴, -X⁵NR¹⁴C(O)NR¹⁴R¹⁴, -X⁵NR¹⁴C(NR¹⁴)NR¹⁴R¹⁴, -X⁵OR¹⁴, -X⁵SR¹⁴, -X⁵C(O)OR¹⁴, 15 -X⁵C(O)NR¹⁴R¹⁴, -X⁵S(O)₂NR¹⁴R¹⁴, -X⁵P(O)(OR¹⁴)OR¹⁴, -X⁵OP(O)(OR¹⁴)OR¹⁴, -X⁵NR¹⁴C(O)R¹⁵, -X⁵S(O)R¹⁵, -X⁵S(O)₂R¹⁵ and -X⁵C(O)R¹⁵, wherein X⁵, R¹⁴ and R¹⁵ are as defined above; or 20 R¹² together with R⁹ and/or R¹³ together with R¹⁰ form trimethylene, tetramethylene or phenylene-1,2-dimethylene, , optionally substituted with 1 to 3 radicals independently selected from (C₁₋₆)alkyl, (C₁₋₆)alkylidene, cyano, halo, halo-substituted (C₁₋₄)alkyl, nitro, oxo, -X⁵NR¹⁴C(O)OR¹⁴, -X⁵NR¹⁴C(O)NR¹⁴R¹⁴, -X⁵NR¹⁴C(NR¹⁴)NR¹⁴R¹⁴, -X⁵OR¹⁴, -X⁵SR¹⁴, -X⁵C(O)OR¹⁴, -X⁵C(O)NR¹⁴R¹⁴, -X⁵S(O)₂NR¹⁴R¹⁴, -X⁵P(O)(OR¹⁴)OR¹⁴, -X⁵OP(O)(OR¹⁴)OR¹⁴, -X⁵NR¹⁴C(O)R¹⁵, 25 -X⁵S(O)R¹⁵, -X⁵S(O)₂R¹⁵ and -X⁵C(O)R¹⁵, wherein X⁵, R¹⁴ and R¹⁵ are as defined above; and R¹ is -X⁶X⁷R²⁰, wherein X⁶ is -C(O)-, -C(O)C(O)- or -S(O)₂-, X⁷ is a bond, -O- or -NR²¹-, wherein R²¹ is hydrogen or (C₁₋₆)alkyl, and R²⁰ is (i) (C₁₋₆)alkyl optionally substituted by cyano, halo, nitro, -NR¹⁴R¹⁴, -NR¹⁴C(O)OR¹⁴, -NR¹⁴C(O)NR¹⁴R¹⁴, -NR¹⁴C(NR¹⁴)NR¹⁴R¹⁴, 30 -OR¹⁴, -SR¹⁴, -C(O)OR¹⁴, -C(O)NR¹⁴R¹⁴, -S(O)₂NR¹⁴R¹⁴, -P(O)(OR¹⁴)OR¹⁴, -OP(O)(OR¹⁴)OR¹⁴, -NR¹⁴C(O)R¹⁵, -S(O)R¹⁵, -S(O)₂R¹⁵, -C(O)R¹⁵, -OR²², -SR²², -S(O)R²², -S(O)₂R²², -C(O)R²², -C(O)OR²², -C(O)NR²²R²³, -NR²²R²³, -NR²³C(O)R²², -NR²³C(O)OR²²,

-NR²³C(O)NR²²R²³ or -NR²³C(NR²³)NR²²R²³, wherein R¹⁴ and R¹⁵ are as defined above, R²² is (C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl, hetero(C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl, (C₆₋₁₂)aryl(C₀₋₆)alkyl, hetero(C₅₋₁₂)aryl(C₀₋₆)alkyl, (C₉₋₁₂)bicycloaryl(C₀₋₆)alkyl or hetero(C₈₋₁₂)bicycloaryl(C₀₋₆)alkyl and R²³ at each occurrence independently is hydrogen or (C₁₋₆)alkyl, or

5 (ii) (C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl, hetero(C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl, (C₆₋₁₂)aryl(C₀₋₆)alkyl, diphenyl(C₀₋₆)alkyl, hetero(C₅₋₁₂)aryl(C₀₋₆)alkyl, dihetero(C₅₋₆)aryl(C₀₋₆)alkyl, (C₉₋₁₂)bicycloaryl(C₀₋₆)alkyl or hetero(C₈₋₁₂)bicycloaryl(C₀₋₆)alkyl wherein said cycloalkyl, heterocycloalkyl, aryl or heteroaryl may be substituted by -R²⁴, -X⁵OR²⁴, -X⁵SR²⁴, -X⁵S(O)R²⁴, -X⁵S(O)₂R²⁴, -X⁵C(O)R²⁴, -X⁵C(O)OR²⁴, -X⁵C(O)NR²⁴R²⁵, -X⁵NR²⁴R²⁵, -X⁵NR²⁵C(O)R²⁴,

10 -X⁵NR²⁵C(O)OR²⁴, -X⁵NR²⁵C(O)NR²⁴R²⁵ or -X⁵NR²⁵C(NR²⁵)NR²⁴R²⁵, wherein X⁵ is as defined above, R²⁴ is (C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl, hetero(C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl, (C₆₋₁₂)aryl(C₀₋₆)alkyl, hetero(C₅₋₁₂)aryl(C₀₋₆)alkyl, (C₉₋₁₂)bicycloaryl(C₀₋₆)alkyl or hetero(C₈₋₁₂)bicycloaryl(C₀₋₆)alkyl and R²⁵ at each occurrence independently is hydrogen or (C₁₋₆)alkyl; wherein within R¹ any alicyclic or aromatic ring system present may be substituted

15 further by 1 to 5 radicals independently selected from (C₁₋₆)alkyl, (C₁₋₆)alkylidene, cyano, halo, halo-substituted (C₁₋₄)alkyl, nitro, -X⁵NR¹⁴R¹⁴, -X⁵NR¹⁴C(O)OR¹⁴, -X⁵NR¹⁴C(O)NR¹⁴R¹⁴, -X⁵NR¹⁴C(NR¹⁴)NR¹⁴R¹⁴, -X⁵OR¹⁴, -X⁵SR¹⁴, -X⁵C(O)OR¹⁴, -X⁵C(O)NR¹⁴R¹⁴, -X⁵S(O)₂NR¹⁴R¹⁴, -X⁵P(O)(OR¹⁴)OR¹⁴, -X⁵OP(O)(OR¹⁴)OR¹⁴, -X⁵NR¹⁴C(O)R¹⁵, -X⁵S(O)R¹⁵, -X⁵S(O)₂R¹⁵ and -X⁵C(O)R¹⁵, wherein X⁵, R¹⁴ and R¹⁵ are as defined above; or when X² is a

20 divalent group of formula (a) or (b) then R¹ may also represent hydrogen, carboxy, oxalo or carbamoyl;

R² is hydrogen or (C₁₋₆)alkyl;

R³ is (i) (C₁₋₆)alkyl optionally substituted with cyano, halo, nitro, -SR²⁴, -C(O)OR²⁴, -C(O)NR²⁴R²⁴, -P(O)(OR²⁴)OR²⁴, -OP(O)(OR²⁴)OR²⁴, -S(O)R²⁵, -S(O)₂R²⁵ or -C(O)R²⁵,

25 wherein R²⁴ at each occurrence independently is hydrogen, (C₁₋₆)alkyl or halo-substituted (C₁₋₃)alkyl and R²⁵ (C₁₋₆)alkyl or halo-substituted (C₁₋₃)alkyl, or (ii) (C₅₋₆)cycloalkyl(C₂₋₃)alkyl, hetero(C₃₋₆)cycloalkyl(C₂₋₃)alkyl, (C₆₋₁₂)aryl(C₂₋₃)alkyl or hetero(C₅₋₆)aryl(C₂₋₃)alkyl, wherein said cycloalkyl, heterocycloalkyl, aryl or heteroaryl optionally is substituted further with 1 to 5 radicals independently selected from (C₁₋₆)alkyl, (C₁₋₆)alkylidene, cyano, halo, halo-substituted

30 (C₁₋₄)alkyl, nitro, -X⁵NR¹⁴C(O)OR¹⁴, -X⁵NR¹⁴C(O)NR¹⁴R¹⁴, -X⁵NR¹⁴C(NR¹⁴)NR¹⁴R¹⁴, -X⁵OR¹⁴, -X⁵SR¹⁴, -X⁵C(O)OR¹⁴, -X⁵C(O)NR¹⁴R¹⁴, -X⁵S(O)₂NR¹⁴R¹⁴, -X⁵P(O)(OR¹⁴)OR¹⁴, -X⁵OP(O)(OR¹⁴)OR¹⁴, -X⁵NR¹⁴C(O)R¹⁵, -X⁵S(O)R¹⁵, -X⁵S(O)₂R¹⁵ and -X⁵C(O)R¹⁵, wherein

X^5 , R^{14} and R^{15} are as defined above, provided that when R^3 is unsubstituted ($C_{1,5}$)alkyl and R^4 is hydrogen or unsubstituted ($C_{1,5}$)alkyl, then X^2 may not represent (i) a bond when R^1 is $-C(O)R^{20}$, $-C(O)_2R^{20}$ or $-S(O)_2R^{20}$ in which R^{20} is ($C_{1,6}$)alkyl, phenyl($C_{1,4}$)alkyl, phenyl, ($C_{3,7}$)cycloalkyl, camphan-10-yl, naphth-1-yl, naphth-2-yl, phenyl substituted by one or more of ($C_{1,4}$)alkyl, perfluoro($C_{1,4}$)alkyl, ($C_{1,4}$)alkoxy, hydroxy, halo, amido, nitro, amino, ($C_{1,4}$)alkylamino, ($C_{1,4}$)dialkylamino, carboxy or ($C_{1,4}$)alkoxycarbonyl, or naphth-1-yl or naphth-2-yl substituted by one or more of ($C_{1,4}$)alkyl, perfluoro($C_{1,4}$)alkyl, ($C_{1,4}$)alkoxy, hydroxy, halo, amido, nitro, amino, carboxy or ($C_{1,4}$)alkoxycarbonyl or (ii) a divalent group of formula (a) or (b) in which the moiety R^{12} is methyl, isopropyl, *n*-butyl, *sec*-butyl, *tert*-butyl, 1-methylpropyl, benzyl, naphth-1-ylmethyl, naphth-2-ylmethyl, thien-2-ylmethyl, thien-3-ylmethyl, or wherein R^9 and R^{12} form ethylene, trimethylene, hydroxy-substituted trimethylene, tetramethylene or phenylene-1,2-dimethylene; or

5 R^3 and R^4 taken together with the carbon atom to which both R^3 and R^4 are attached form ($C_{3,8}$)cycloalkylene or ($C_{3,8}$)heterocycloalkylene, wherein said cycloalkylene or heterocycloalkylene is optionally substituted with 1 to 3 radicals independently selected from ($C_{1,6}$)alkyl, ($C_{1,6}$)alkylidene, cyano, halo, halo-substituted ($C_{1,4}$)alkyl, nitro, $-X^5NR^{14}C(O)OR^{14}$, $-X^5NR^{14}C(O)NR^{14}R^{14}$, $-X^5NR^{14}C(NR^{14})NR^{14}R^{14}$, $-X^5OR^{14}$, $-X^5SR^{14}$, $-X^5C(O)OR^{14}$, $-X^5C(O)NR^{14}R^{14}$, $-X^5S(O)_2NR^{14}R^{14}$, $-X^5P(O)(OR^{14})OR^{14}$, $-X^5OP(O)(OR^{14})OR^{14}$, $-X^5NR^{14}C(O)R^{15}$, $-X^5S(O)R^{15}$, $-X^5S(O)_2R^{15}$ and $-X^5C(O)R^{15}$, wherein X^5 , R^{14} and R^{15} are as defined above;

10 R^3 and R^4 taken together with the carbon atom to which both R^3 and R^4 are attached form ($C_{3,8}$)cycloalkylene or ($C_{3,8}$)heterocycloalkylene, wherein said cycloalkylene or heterocycloalkylene is optionally substituted with 1 to 3 radicals independently selected from ($C_{1,6}$)alkyl, ($C_{1,6}$)alkylidene, cyano, halo, halo-substituted ($C_{1,4}$)alkyl, nitro, $-X^5NR^{14}C(O)OR^{14}$, $-X^5NR^{14}C(O)NR^{14}R^{14}$, $-X^5NR^{14}C(NR^{14})NR^{14}R^{14}$, $-X^5OR^{14}$, $-X^5SR^{14}$, $-X^5C(O)OR^{14}$, $-X^5C(O)NR^{14}R^{14}$, $-X^5S(O)_2NR^{14}R^{14}$, $-X^5P(O)(OR^{14})OR^{14}$, $-X^5OP(O)(OR^{14})OR^{14}$, $-X^5NR^{14}C(O)R^{15}$, $-X^5S(O)R^{15}$, $-X^5S(O)_2R^{15}$ and $-X^5C(O)R^{15}$, wherein X^5 , R^{14} and R^{15} are as defined above;

15 R^3 and R^4 taken together with the carbon atom to which both R^3 and R^4 are attached form ($C_{3,8}$)cycloalkylene or ($C_{3,8}$)heterocycloalkylene, wherein said cycloalkylene or heterocycloalkylene is optionally substituted with 1 to 3 radicals independently selected from ($C_{1,6}$)alkyl, ($C_{1,6}$)alkylidene, cyano, halo, halo-substituted ($C_{1,4}$)alkyl, nitro, $-X^5NR^{14}C(O)OR^{14}$, $-X^5NR^{14}C(O)NR^{14}R^{14}$, $-X^5NR^{14}C(NR^{14})NR^{14}R^{14}$, $-X^5OR^{14}$, $-X^5SR^{14}$, $-X^5C(O)OR^{14}$, $-X^5C(O)NR^{14}R^{14}$, $-X^5S(O)_2NR^{14}R^{14}$, $-X^5P(O)(OR^{14})OR^{14}$, $-X^5OP(O)(OR^{14})OR^{14}$, $-X^5NR^{14}C(O)R^{15}$, $-X^5S(O)R^{15}$, $-X^5S(O)_2R^{15}$ and $-X^5C(O)R^{15}$, wherein X^5 , R^{14} and R^{15} are as defined above;

20 R^3 and R^4 taken together with the carbon atom to which both R^3 and R^4 are attached form ($C_{3,8}$)cycloalkylene or ($C_{3,8}$)heterocycloalkylene, wherein said cycloalkylene or heterocycloalkylene is optionally substituted with 1 to 3 radicals independently selected from ($C_{1,6}$)alkyl, ($C_{1,6}$)alkylidene, cyano, halo, halo-substituted ($C_{1,4}$)alkyl, nitro, $-X^5NR^{14}C(O)OR^{14}$, $-X^5NR^{14}C(O)NR^{14}R^{14}$, $-X^5NR^{14}C(NR^{14})NR^{14}R^{14}$, $-X^5OR^{14}$, $-X^5SR^{14}$, $-X^5C(O)OR^{14}$, $-X^5C(O)NR^{14}R^{14}$, $-X^5S(O)_2NR^{14}R^{14}$, $-X^5P(O)(OR^{14})OR^{14}$, $-X^5OP(O)(OR^{14})OR^{14}$, $-X^5NR^{14}C(O)R^{15}$, $-X^5S(O)R^{15}$, $-X^5S(O)_2R^{15}$ and $-X^5C(O)R^{15}$, wherein X^5 , R^{14} and R^{15} are as defined above;

25 R^4 is hydrogen, ($C_{1,6}$)alkyl or as defined above;

R^5 is hydrogen and R^6 is hydroxy or R^5 and R^6 together form oxo;

30 R^7 is a group selected from cyano, halo, nitro, $-R^{29}$, $-X^5NR^{29}R^{30}$, $-X^5NR^{30}C(O)OR^{29}$, $-X^5NR^{30}C(O)NR^{29}R^{30}$, $-X^5NR^{30}C(NR^{30})NR^{29}R^{30}$, $-X^5OR^{29}$, $-X^5SR^{29}$, $-X^5C(O)OR^{29}$, $-X^5C(O)NR^{29}R^{30}$, $-X^5S(O)_2NR^{29}R^{30}$, $-X^5P(O)(OR^{30})OR^{29}$, $-X^5OP(O)(OR^{29})OR^{29}$,

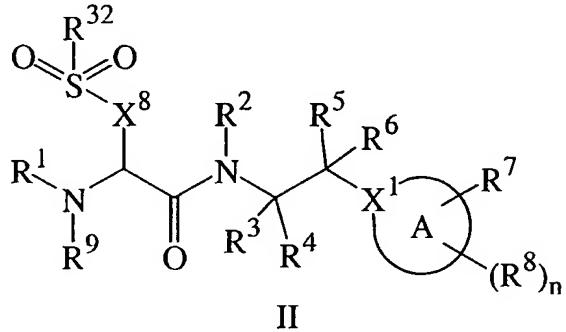
-X⁵NR³⁰C(O)R²⁰, -X⁵S(O)R²⁰, -X⁵S(O)₂R²⁰, -X⁵C(O)R²⁰ and -C(O)NR⁴²CHR⁴³C(O)OR²⁹, wherein X⁵ and R²⁰ are as defined as above, R²⁹ is hydrogen or -R²⁰, wherein R²⁰ is defined as above, R³⁰ at each occurrence is hydrogen or (C₁₋₆)alkyl, R⁴² is hydrogen, (C₁₋₆)alkyl or together with R⁴³ forms trimethylene, tetramethylene or phenylene-1,2-dimethylene, optionally substituted with hydroxy or oxo, and R⁴³ is as defined above or is (i) (C₁₋₆)alkyl optionally substituted with cyano, halo, nitro, -NR¹⁴R¹⁴, -NR¹⁴C(O)OR¹⁴, -NR¹⁴C(O)NR¹⁴R¹⁴, -NR¹⁴C(NR¹⁴)NR¹⁴R¹⁴, -OR¹⁴, -SR¹⁴, -C(O)OR¹⁴, -C(O)NR¹⁴R¹⁴, -S(O)₂NR¹⁴R¹⁴, -P(O)(OR¹⁴)OR¹⁴, -OP(O)(OR¹⁴)OR¹⁴, -NR¹⁴C(O)R¹⁵, -S(O)R¹⁵, -S(O)₂R¹⁵, -C(O)R¹⁵, -OR¹⁶, -SR¹⁶, -S(O)R¹⁶, -S(O)₂R¹⁶, -C(O)R¹⁶, -C(O)OR¹⁶, -OC(O)R¹⁶, -NR¹⁶R¹⁷, -NR¹⁷C(O)R¹⁶, -NR¹⁷C(O)OR¹⁶, -C(O)NR¹⁶R¹⁷, -S(O)₂NR¹⁶R¹⁷, -NR¹⁷C(O)NR¹⁶R¹⁷ or -NR¹⁷C(NR¹⁷)NR¹⁶R¹⁷ or (ii) a group selected from (C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl, hetero(C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl, (C₆₋₁₂)aryl(C₀₋₆)alkyl, hetero(C₅₋₁₂)aryl(C₀₋₆)alkyl, (C₉₋₁₂)polycycloaryl(C₀₋₆)alkyl and hetero(C₈₋₁₂)polycycloaryl(C₀₋₆)alkyl, wherein said cycloalkyl, heterocycloalkyl, aryl, heteroaryl, polycycloaryl or heteropolycycloaryl ring optionally is substituted by a group selected from -R¹⁸, -X⁵OR¹⁸, -X⁵SR¹⁸, -X⁵S(O)R¹⁸, -X⁵S(O)₂R¹⁸, -X⁵C(O)R¹⁸, -X⁵C(O)OR¹⁸, -X⁵OC(O)R¹⁸, -X⁵NR¹⁸R¹⁹, -X⁵NR¹⁹C(O)R¹⁸, -X⁵NR¹⁹C(O)OR¹⁸, -X⁵C(O)NR¹⁸R¹⁹, -X⁵S(O)₂NR¹⁸R¹⁹, -X⁵NR¹⁹C(O)NR¹⁸R¹⁹ or -X⁵NR¹⁹C(NR¹⁹)NR¹⁸R¹⁹, wherein X⁵, R¹⁴, R¹⁵, R¹⁶, R¹⁷, R¹⁸ and R¹⁹ are as defined above; wherein within R⁷ any alicyclic or aromatic ring system present may be substituted further by 1 to 5 radicals independently selected from (C₁₋₆)alkyl, (C₁₋₆)alkylidene, cyano, halo, halo-substituted (C₁₋₄)alkyl, nitro, -X⁵NR¹⁴R¹⁴, -X⁵NR¹⁴C(O)OR¹⁴, -X⁵NR¹⁴C(O)NR¹⁴R¹⁴, -X⁵NR¹⁴C(NR¹⁴)NR¹⁴R¹⁴, -X⁵OR¹⁴, -X⁵SR¹⁴, -X⁵C(O)OR¹⁴, -X⁵C(O)NR¹⁴R¹⁴, -X⁵S(O)₂NR¹⁴R¹⁴, -X⁵P(O)(OR¹⁴)OR¹⁴, -X⁵OP(O)(OR¹⁴)OR¹⁴, -X⁵NR¹⁴C(O)R¹⁵, -X⁵S(O)R¹⁵, -X⁵S(O)₂R¹⁵ and -X⁵C(O)R¹⁵, wherein X⁵, R¹⁴ and R¹⁵ are as defined above; and

R⁸ at each occurrence independently is selected from (C₁₋₆)alkyl, halo-substituted (C₁₋₄)alkyl, (C₁₋₆)alkylidene, cyano, halo, halo-substituted (C₁₋₄)alkyl, nitro, -X⁵NR¹⁴R¹⁴, -X⁵NR¹⁴C(O)OR¹⁴, -X⁵NR¹⁴C(O)NR¹⁴R¹⁴, -X⁵NR¹⁴C(NR¹⁴)NR¹⁴R¹⁴, -X⁵OR¹⁴, -X⁵SR¹⁴, -X⁵C(O)OR¹⁴, -X⁵C(O)NR¹⁴R¹⁴, -X⁵S(O)₂NR¹⁴R¹⁴, -X⁵P(O)(OR¹⁴)OR¹⁴, -X⁵OP(O)(OR¹⁴)OR¹⁴, -X⁵NR¹⁴C(O)R¹⁵, -X⁵S(O)R¹⁵, -X⁵S(O)₂R¹⁵ and -X⁵C(O)R¹⁵, wherein

X⁵ is a bond or (C₁₋₆)alkylene, R¹⁴ at each occurrence independently is hydrogen, (C₁₋₆)alkyl or halo-substituted (C₁₋₃)alkyl and R¹⁵ (C₁₋₆)alkyl or halo-substituted (C₁₋₃)alkyl; and the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of

isomers; and the pharmaceutically acceptable salts thereof.

In another particular embodiment, the present invention relates to a compound of Formula II:



5 in which:

A comprises a heteromonocyclic ring containing 5 to 6 ring member atoms or a fused heteropolycyclic ring system containing 8 to 14 ring member atoms, wherein each ring contains 5 to 7 ring member atoms, X¹ is a ring member carbon atom and each ring member atom other than X¹ is a carbon atom or a heteroatom, with the proviso that at least one ring member atom is 10 a heteroatom;

n is 0, 1, 2 or 3;

X¹ is =C- or -CH-;

X⁸ is (C₁₋₂)alkylene;

R¹ is hydrogen, carboxy, oxalo, carbamoyl or -X⁶X⁷R²⁰, wherein X⁶ is -C(O)-,

15 -C(O)C(O)- or -S(O)₂-, X⁷ is a bond, -O- or -NR²¹-, wherein R²¹ is hydrogen or (C₁₋₆)alkyl, and R²⁰ is (i) (C₁₋₆)alkyl optionally substituted by cyano, halo, nitro, -NR¹⁴R¹⁴, -NR¹⁴C(O)OR¹⁴, -NR¹⁴C(O)NR¹⁴R¹⁴, -NR¹⁴C(NR¹⁴)NR¹⁴R¹⁴, -OR¹⁴, -SR¹⁴, -C(O)OR¹⁴, -C(O)NR¹⁴R¹⁴, -S(O)₂NR¹⁴R¹⁴, -P(O)(OR¹⁴)OR¹⁴, -OP(O)(OR¹⁴)OR¹⁴, -NR¹⁴C(O)R¹⁵, -S(O)R¹⁵, -S(O)₂R¹⁵, -C(O)R¹⁵, -OR²², -SR²², -S(O)R²², -S(O)₂R²², -C(O)R²², -C(O)OR²², -C(O)NR²²R²³, 20 -NR²²R²³, -NR²³C(O)R²², -NR²³C(O)OR²², -NR²³C(O)NR²²R²³ or -NR²³C(NR²³)NR²²R²³, wherein R¹⁴ at each occurrence independently is hydrogen, (C₁₋₆)alkyl or halo-substituted (C₁₋₃)alkyl, R¹⁵ is (C₁₋₆)alkyl or halo-substituted (C₁₋₃)alkyl, R²² is (C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl, hetero(C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl, (C₆₋₁₂)aryl(C₀₋₆)alkyl, hetero(C₅₋₁₂)aryl(C₀₋₆)alkyl, (C₉₋₁₂)bicycloaryl(C₀₋₆)alkyl or hetero(C₈₋₁₂)bicycloaryl(C₀₋₆)alkyl and R²³ at each occurrence 25 independently is hydrogen or (C₁₋₆)alkyl, or (ii) (C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl,

hetero(C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl, (C₆₋₁₂)aryl(C₀₋₆)alkyl, hetero(C₅₋₁₂)aryl(C₀₋₆)alkyl, (C₉₋₁₂)bicycloaryl(C₀₋₆)alkyl or hetero(C₈₋₁₂)bicycloaryl(C₀₋₆)alkyl or
 (iii) (C₃₋₆)cycloalkyl(C₀₋₆)alkyl, hetero(C₃₋₆)cycloalkyl(C₀₋₆)alkyl, phenyl(C₀₋₆)alkyl or
 hetero(C₅₋₆)aryl(C₀₋₆)alkyl substituted by -X⁵OR²⁴, -X⁵SR²⁴, -X⁵S(O)R²⁴, -X⁵S(O)₂R²⁴,
 5 -X⁵C(O)R²⁴, -X⁵C(O)OR²⁴, -X⁵C(O)NR²⁴R²⁵, -X⁵NR²⁴R²⁵, -X⁵NR²⁵C(O)R²⁴,
 -X⁵NR²⁵C(O)OR²⁴, -X⁵NR²⁵C(O)NR²⁴R²⁵ or -X⁵NR²⁵C(NR²⁵)NR²⁴R²⁵, wherein X⁵ is a bond
 or (C₁₋₆)alkylene, R²⁴ is (C₃₋₆)cycloalkyl(C₀₋₆)alkyl, hetero(C₃₋₆)cycloalkyl(C₀₋₆)alkyl,
 phenyl(C₀₋₆)alkyl or hetero(C₅₋₆)aryl(C₀₋₆)alkyl and R²⁵ at each occurrence independently is
 hydrogen or (C₁₋₆)alkyl; wherein within R¹ any alicyclic or aromatic ring system present may be
 10 substituted further by 1 to 5 radicals independently selected from (C₁₋₆)alkyl, (C₁₋₆)alkylidene,
 cyano, halo, halo-substituted (C₁₋₄)alkyl, nitro, -X⁵NR¹⁴R¹⁴, -X⁵NR¹⁴C(O)OR¹⁴,
 -X⁵NR¹⁴C(O)NR¹⁴R¹⁴, -X⁵NR¹⁴C(NR¹⁴)NR¹⁴R¹⁴, -X⁵OR¹⁴, -X⁵SR¹⁴, -X⁵C(O)OR¹⁴,
 -X⁵C(O)NR¹⁴R¹⁴, -X⁵S(O)₂NR¹⁴R¹⁴, -X⁵P(O)(OR¹⁴)OR¹⁴, -X⁵OP(O)(OR¹⁴)OR¹⁴,
 -X⁵NR¹⁴C(O)R¹⁵, -X⁵S(O)R¹⁵, -X⁵S(O)₂R¹⁵ and -X⁵C(O)R¹⁵, wherein X⁵, R¹⁴ and R¹⁵ are as
 15 defined above;

R² is hydrogen or (C₁₋₆)alkyl;

R³ is (i) (C₁₋₆)alkyl optionally substituted with cyano, halo, nitro, -NR¹⁴R¹⁴,
 -NR¹⁴C(O)OR¹⁴, -NR¹⁴C(O)NR¹⁴R¹⁴, -NR¹⁴C(NR¹⁴)NR¹⁴R¹⁴, -OR¹⁴, -SR¹⁴, -C(O)OR¹⁴,
 -C(O)NR¹⁴R¹⁴, -S(O)₂NR¹⁴R¹⁴, -P(O)(OR¹⁴)OR¹⁴, -OP(O)(OR¹⁴)OR¹⁴, -NR¹⁴C(O)R¹⁵,
 20 -S(O)R¹⁵, -S(O)₂R¹⁵, -C(O)R¹⁵, -OR¹⁶, -SR¹⁶, -S(O)R¹⁶, -S(O)₂R¹⁶, -C(O)R¹⁶, -C(O)OR¹⁶,
 -OC(O)R¹⁶, -NR¹⁶R¹⁷, -NR¹⁷C(O)R¹⁶, -NR¹⁷C(O)OR¹⁶, -C(O)NR¹⁶R¹⁷, -S(O)₂NR¹⁶R¹⁷,
 -NR¹⁷C(O)NR¹⁶R¹⁷ or -NR¹⁷C(NR¹⁷)NR¹⁶R¹⁷, wherein R¹⁴ at each occurrence independently
 is hydrogen, (C₁₋₆)alkyl or halo-substituted (C₁₋₃)alkyl, R¹⁵ is (C₁₋₆)alkyl or halo-substituted
 (C₁₋₃)alkyl, R¹⁶ is (C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl, hetero(C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl,
 25 (C₆₋₁₂)aryl(C₀₋₆)alkyl, hetero(C₅₋₁₂)aryl(C₀₋₆)alkyl, (C₉₋₁₂)polycycloaryl(C₀₋₆)alkyl or
 hetero(C₈₋₁₂)polycycloaryl(C₀₋₆)alkyl and R¹⁷ is hydrogen or (C₁₋₆)alkyl, and wherein within R¹⁶
 said cycloalkyl, heterocycloalkyl, aryl, heteroaryl, polycycloaryl or heteropolycycloaryl ring
 optionally is substituted by a group selected from -R¹⁸, -X⁵OR¹⁸, -X⁵SR¹⁸, -X⁵S(O)R¹⁸,
 -X⁵S(O)₂R¹⁸, -X⁵C(O)R¹⁸, -X⁵C(O)OR¹⁸, -X⁵OC(O)R¹⁸, -X⁵NR¹⁸R¹⁹, -X⁵NR¹⁹C(O)R¹⁸,
 30 -X⁵NR¹⁹C(O)OR¹⁸, -X⁵C(O)NR¹⁸R¹⁹, -X⁵S(O)₂NR¹⁸R¹⁹, -X⁵NR¹⁹C(O)NR¹⁸R¹⁹ or
 -X⁵NR¹⁹C(NR¹⁹)NR¹⁸R¹⁹, wherein X⁵ is as defined above, R¹⁸ is hydrogen or (C₁₋₆)alkyl and
 R¹⁹ is (C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl, hetero(C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl, (C₆₋₁₂)aryl(C₀₋₆)alkyl,

hetero(C₅₋₁₂)aryl(C₀₋₆)alkyl, (C₉₋₁₂)polycycloaryl(C₀₋₆)alkyl or
 hetero(C₈₋₁₂)polycycloaryl(C₀₋₆)alkyl, or (ii) a group selected from (C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl,
 hetero(C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl, (C₆₋₁₂)aryl(C₀₋₆)alkyl, hetero(C₅₋₁₂)aryl(C₀₋₆)alkyl,
 (C₉₋₁₂)polycycloaryl(C₀₋₆)alkyl and hetero(C₈₋₁₂)polycycloaryl(C₀₋₆)alkyl, wherein said cycloalkyl,

5 heterocycloalkyl, aryl, heteroaryl, polycycloaryl or heteropolycycloaryl ring optionally is
 substituted by a group selected from -R¹⁸, -X⁵OR¹⁸, -X⁵SR¹⁸, -X⁵S(O)R¹⁸, -X⁵S(O)₂R¹⁸,
 -X⁵C(O)R¹⁸, -X⁵C(O)OR¹⁸, -X⁵OC(O)R¹⁸, -X⁵NR¹⁸R¹⁹, -X⁵NR¹⁹C(O)R¹⁸, -X⁵NR¹⁹C(O)OR¹⁸,
 -X⁵C(O)NR¹⁸R¹⁹, -X⁵S(O)₂NR¹⁸R¹⁹, -X⁵NR¹⁹C(O)NR¹⁸R¹⁹ or -X⁵NR¹⁹C(NR¹⁹)NR¹⁸R¹⁹,
 wherein X⁵, R¹⁸ and R¹⁹ are as defined above; wherein within R¹² and/or R¹³ any alicyclic or

10 aromatic ring system present may be substituted further by 1 to 5 radicals independently
 selected from (C₁₋₆)alkyl, (C₁₋₆)alkylidene, cyano, halo, halo-substituted (C₁₋₄)alkyl, nitro,
 -X⁵NR¹⁴R¹⁴, -X⁵NR¹⁴C(O)OR¹⁴, -X⁵NR¹⁴C(O)NR¹⁴R¹⁴, -X⁵NR¹⁴C(NR¹⁴)NR¹⁴R¹⁴, -X⁵OR¹⁴,
 -X⁵SR¹⁴, -X⁵C(O)OR¹⁴, -X⁵C(O)NR¹⁴R¹⁴, -X⁵S(O)₂NR¹⁴R¹⁴, -X⁵P(O)(OR¹⁴)OR¹⁴,
 -X⁵OP(O)(OR¹⁴)OR¹⁴, -X⁵NR¹⁴C(O)R¹⁵, -X⁵S(O)R¹⁵, -X⁵S(O)₂R¹⁵ and -X⁵C(O)R¹⁵, wherein

15 X⁵, R¹⁴ and R¹⁵ are as defined above, or

R³ and R⁴ taken together with the carbon atom to which both R³ and R⁴ are attached
 form (C₃₋₈)cycloalkylene or (C₃₋₈)heterocycloalkylene, wherein said cycloalkylene or
 heterocycloalkylene is optionally substituted with 1 to 3 radicals independently selected from
 (C₁₋₆)alkyl, (C₁₋₆)alkylidene, cyano, halo, halo-substituted (C₁₋₄)alkyl, nitro, -X⁵NR¹⁴C(O)OR¹⁴,

20 -X⁵NR¹⁴C(O)NR¹⁴R¹⁴, -X⁵NR¹⁴C(NR¹⁴)NR¹⁴R¹⁴, -X⁵OR¹⁴, -X⁵SR¹⁴, -X⁵C(O)OR¹⁴,
 -X⁵C(O)NR¹⁴R¹⁴, -X⁵S(O)₂NR¹⁴R¹⁴, -X⁵P(O)(OR¹⁴)OR¹⁴, -X⁵OP(O)(OR¹⁴)OR¹⁴,
 -X⁵NR¹⁴C(O)R¹⁵, -X⁵S(O)R¹⁵, -X⁵S(O)₂R¹⁵ and -X⁵C(O)R¹⁵, wherein X⁵, R¹⁴ and R¹⁵ are as
 defined above;

R⁴ is hydrogen, (C₁₋₆)alkyl or as defined above;

25 R⁵ is hydrogen and R⁶ is hydroxy or R⁵ and R⁶ together form oxo;
 R⁷ is a group selected from cyano, halo, nitro, -R²⁹, -X⁵NR²⁹R³⁰, -X⁵NR³⁰C(O)OR²⁹,
 -X⁵NR³⁰C(O)NR²⁹R³⁰, -X⁵NR³⁰C(NR³⁰)NR²⁹R³⁰, -X⁵OR²⁹, -X⁵SR²⁹, -X⁵C(O)OR²⁹,
 -X⁵C(O)NR²⁹R³⁰, -X⁵S(O)₂NR²⁹R³⁰, -X⁵P(O)(OR³⁰)OR²⁹, -X⁵OP(O)(OR²⁹)OR²⁹,
 -X⁵NR³⁰C(O)R³¹, -X⁵S(O)R³¹, -X⁵S(O)₂R³¹ and -X⁵C(O)R³¹, wherein X⁵ is as defined above,

30 R²⁹ is hydrogen or -R³¹, R³⁰ at each occurrence is hydrogen or (C₁₋₆)alkyl and R³¹ is (C₁₋₆)alkyl,
 (C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl, hetero(C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl, (C₆₋₁₂)aryl(C₀₋₆)alkyl or
 hetero(C₅₋₁₂)aryl(C₀₋₆)alkyl, wherein within R⁷ any alicyclic or aromatic ring system present may

be substituted further by 1 to 5 radicals independently selected from (C₁₋₆)alkyl, (C₁₋₆)alkylidene, cyano, halo, halo-substituted (C₁₋₄)alkyl, nitro, -X⁵NR¹⁴R¹⁴, -X⁵NR¹⁴C(O)OR¹⁴, -X⁵NR¹⁴C(O)NR¹⁴R¹⁴, -X⁵NR¹⁴C(NR¹⁴)NR¹⁴R¹⁴, -X⁵OR¹⁴, -X⁵SR¹⁴, -X⁵C(O)OR¹⁴, -X⁵C(O)NR¹⁴R¹⁴, -X⁵S(O)₂NR¹⁴R¹⁴, -X⁵P(O)(OR¹⁴)OR¹⁴, -X⁵OP(O)(OR¹⁴)OR¹⁴,

5 -X⁵NR¹⁴C(O)R¹⁵, -X⁵S(O)R¹⁵, -X⁵S(O)₂R¹⁵ and -X⁵C(O)R¹⁵, wherein X⁵, R¹⁴ and R¹⁵ are as defined above; and

R⁸ at each occurrence independently is selected from (C₁₋₆)alkyl, (C₁₋₆)alkylidene, cyano, halo, halo-substituted (C₁₋₄)alkyl, nitro, -X⁵NR¹⁴R¹⁴, -X⁵NR¹⁴C(O)OR¹⁴, -X⁵NR¹⁴C(O)NR¹⁴R¹⁴, -X⁵NR¹⁴C(NR¹⁴)NR¹⁴R¹⁴, -X⁵OR¹⁴, -X⁵SR¹⁴, -X⁵C(O)OR¹⁴, -X⁵C(O)NR¹⁴R¹⁴, -X⁵S(O)₂NR¹⁴R¹⁴, -X⁵P(O)(OR¹⁴)OR¹⁴, -X⁵OP(O)(OR¹⁴)OR¹⁴, -X⁵NR¹⁴C(O)R¹⁵, -X⁵S(O)R¹⁵, -X⁵S(O)₂R¹⁵ and -X⁵C(O)R¹⁵, wherein X⁵, R¹⁴ and R¹⁵ are as defined above;

R⁹ is hydrogen or (C₁₋₆)alkyl; and

R³² is (C₁₋₈)alkyl, (C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl, hetero(C₃₋₁₂)cycloalkyl(C₀₋₆)alkyl,

15 (C₆₋₁₂)aryl(C₀₋₆)alkyl, hetero(C₅₋₁₂)aryl(C₀₋₆)alkyl, (C₉₋₁₂)polycycloaryl(C₀₋₆)alkyl or hetero(C₈₋₁₂)polycycloaryl(C₀₋₆)alkyl, wherein within R³⁰ any alicyclic or aromatic ring system present may be substituted further by 1 to 5 radicals independently selected from (C₁₋₆)alkyl, (C₁₋₆)alkylidene, cyano, halo, halo-substituted (C₁₋₄)alkyl, nitro, -X⁵NR¹⁴R¹⁴, -X⁵NR¹⁴C(O)OR¹⁴, -X⁵NR¹⁴C(O)NR¹⁴R¹⁴, -X⁵NR¹⁴C(NR¹⁴)NR¹⁴R¹⁴, -X⁵OR¹⁴, -X⁵SR¹⁴, -X⁵C(O)OR¹⁴, -X⁵C(O)NR¹⁴R¹⁴, -X⁵S(O)₂NR¹⁴R¹⁴, -X⁵P(O)(OR¹⁴)OR¹⁴, -X⁵OP(O)(OR¹⁴)OR¹⁴, -X⁵NR¹⁴C(O)R¹⁵, -X⁵S(O)R¹⁵, -X⁵S(O)₂R¹⁵ and -X⁵C(O)R¹⁵, wherein X⁵, R¹⁴ and R¹⁵ are as defined above; and the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers; and the pharmaceutically acceptable salts thereof.

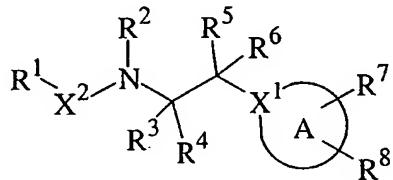
In another particular embodiment, the present invention relates to a pharmaceutical composition which contains a compound of Formula I or II, or a N-oxide derivative, prodrug derivative, individual isomer or mixture of isomers, or a pharmaceutically acceptable salt thereof in admixture with one or more suitable excipients.

In another particular embodiment, the present invention relates to method of treating a disease in an animal in which inhibition of a cysteine protease can prevent, inhibit or ameliorate the pathology and/or symptomatology of the disease, which method comprises administering to the animal a therapeutically effective amount of compound of Formula I or II or a N-oxide derivative, prodrug derivative, individual isomer or mixture of isomers or a pharmaceutically

acceptable salt thereof.

In another particular embodiment, the present invention relates to processes for preparing compounds of Formula I and II and the *N*-oxide derivatives, prodrug derivative, protected derivatives, individual isomers and mixtures of isomers, and the pharmaceutically acceptable salts thereof as set forth in "Detailed Description of the Invention".

In another particular embodiment, the present invention relates to protease inhibitors of Formula III:



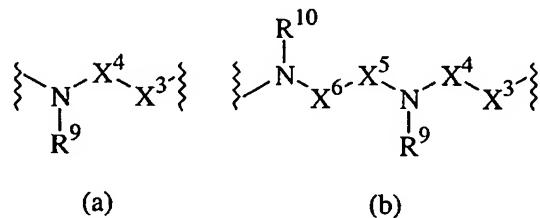
III

in which:

10 A comprises a heteromonocyclic radical containing 5 to 6 annular atoms or a fused heteropolycyclic radical containing 8 to 14 annular atoms, wherein each ring contains 5 to 7 annular atoms, X¹ is an annular carbon atom and each annular atom other than X¹ optionally is a heteroatom, with the proviso that when A is a heteromonocyclic radical containing 5 annular atoms, no more than two of the annular atoms comprising the ring are heteroatoms;

15 X¹ is selected from =C- and -CH-;

X² is a bond or a divalent group of Formula (a) or (b):



wherein:

X³ and X⁵ independently are -C(O)- or -S(O)₂-,

20 X⁴ is -CHR¹¹-, -CH₂CHR¹¹- or -CHR¹¹CH₂- and X⁶ is -CHR¹²-, -CH₂CHR¹²- or -CHR¹²CH₂- wherein:

R¹¹ and R¹² are independently (i) (C₁₋₆)alkyl or halo-substituted(C₁₋₆)alkyl optionally substituted with -OR¹³, -SR¹³, -S(O)R¹³,

$\text{-S(O)}_2\text{R}^{13}$, -C(O)R^{13} , -C(O)OR^{13} , $\text{-NR}^{13}\text{R}^{14}$, $\text{-NR}^{14}\text{C(O)OR}^{13}$, $\text{-C(O)NR}^{13}\text{R}^{14}$,
 $\text{-S(O)}_2\text{NR}^{13}\text{R}^{14}$, $\text{-NR}^{14}\text{C(O)NR}^{13}\text{R}^{14}$ or $\text{-NR}^{14}\text{C(NR}^{14}\text{)NR}^{13}\text{R}^{14}$, wherein R^{13} is
hydrogen, $(\text{C}_{1-6})\text{alkyl}$, $(\text{C}_{3-12})\text{cycloalkyl}(\text{C}_{0-3})\text{alkyl}$,
hetero $(\text{C}_{3-12})\text{cycloalkyl}(\text{C}_{0-3})\text{alkyl}$, $(\text{C}_{6-12})\text{aryl}(\text{C}_{0-3})\text{alkyl}$ or
hetero $(\text{C}_{5-12})\text{aryl}(\text{C}_{0-3})\text{alkyl}$ and R^{14} is hydrogen or $(\text{C}_{1-6})\text{alkyl}$, or
5 (ii) $(\text{C}_{3-12})\text{cycloalkyl}(\text{C}_{0-3})\text{alkyl}$, hetero $(\text{C}_{3-12})\text{cycloalkyl}(\text{C}_{0-3})\text{alkyl}$,
 $(\text{C}_{6-12})\text{aryl}(\text{C}_{0-3})\text{alkyl}$, hetero $(\text{C}_{5-12})\text{aryl}(\text{C}_{0-3})\text{alkyl}$, $(\text{C}_{9-12})\text{polycycloaryl}(\text{C}_{0-3})\text{alkyl}$
or hetero $(\text{C}_{8-12})\text{polycycloaryl}(\text{C}_{0-3})\text{alkyl}$ optionally substituted with -R^{15} ,
 $\text{-X}^7\text{OR}^{15}$, $\text{-X}^7\text{SR}^{15}$, -S(O)R^{15} , $\text{-S(O)}_2\text{R}^{15}$, -C(O)R^{15} , -C(O)OR^{15} , $\text{-X}^7\text{NR}^{15}\text{R}^{16}$,
10 $\text{-X}^7\text{NR}^{16}\text{C(O)OR}^{15}$, $\text{-C(O)NR}^{15}\text{R}^{16}$, $\text{-S(O)}_2\text{NR}^{15}\text{R}^{16}$, $\text{-NR}^{16}\text{C(O)NR}^{15}\text{R}^{16}$ or
 $\text{-NR}^{16}\text{C(NR}^{16}\text{)NR}^{15}\text{R}^{16}$, wherein X^7 is a bond or methylene, R^{15} is
 $(\text{C}_{3-12})\text{cycloalkyl}(\text{C}_{0-3})\text{alkyl}$, hetero $(\text{C}_{3-12})\text{cycloalkyl}(\text{C}_{0-3})\text{alkyl}$,
 $(\text{C}_{6-12})\text{aryl}(\text{C}_{0-3})\text{alkyl}$, hetero $(\text{C}_{5-12})\text{aryl}(\text{C}_{0-3})\text{alkyl}$, $(\text{C}_{9-12})\text{polycycloaryl}(\text{C}_{0-3})\text{alkyl}$
or hetero $(\text{C}_{8-12})\text{polycycloaryl}(\text{C}_{0-3})\text{alkyl}$ and R^{16} is hydrogen or $(\text{C}_{1-6})\text{alkyl}$, or
15 (iii) together with R^9 or R^{10} , respectively, when X^4 is -CHR^{11-} and/or X^6 is
 -CHR^{12-} , forms trimethylene, tetramethylene or phenylene-1,2-dimethylene,
optionally substituted with hydroxy or oxo; wherein any 1 to 3 annular atoms of
any aromatic ring with available valences comprising R^{11} and/or R^{12} are
optionally independently substituted with halo, nitro, cyano, $(\text{C}_{1-6})\text{alkyl}$,
20 halo-substituted $(\text{C}_{1-6})\text{alkyl}$, -OR^{17} , -C(O)R^{17} , -C(O)OR^{17} , $\text{-C(O)NR}^{17}\text{R}^{17}$,
 $\text{-S(O)}_2\text{NR}^{17}\text{R}^{17}$, $\text{-X}^7\text{NR}^{17}\text{R}^{17}$, $\text{-X}^7\text{NR}^{17}\text{C(O)OR}^{17}$, $\text{-X}^7\text{NR}^{17}\text{C(O)NR}^{17}\text{R}^{17}$ or
 $\text{-X}^7\text{NR}^{17}\text{C(NR}^{17}\text{)NR}^{17}\text{R}^{17}$, wherein X^7 is as defined above and each R^{17}
independently is hydrogen or $(\text{C}_{1-6})\text{alkyl}$; and
25 R^9 and R^{10} are independently hydrogen, $(\text{C}_{1-6})\text{alkyl}$ or as defined above;
 R^1 is hydrogen or $\text{-X}^8\text{X}^9\text{R}^{18}$, wherein X^8 is -C(O)- or -S(O)_2- , X^9 is a bond, -O- or
 -NR^{19-} , wherein R^{19} is hydrogen or $(\text{C}_{1-6})\text{alkyl}$, and R^{18} is (i) $(\text{C}_{1-6})\text{alkyl}$ or
halo-substituted $(\text{C}_{1-6})\text{alkyl}$ optionally substituted with -OR^{13} , -SR^{13} , -S(O)R^{13} , $\text{-S(O)}_2\text{R}^{13}$,
 -C(O)R^{13} , -C(O)OR^{13} , $\text{-NR}^{13}\text{R}^{14}$, $\text{-NR}^{14}\text{C(O)OR}^{13}$, $\text{-C(O)NR}^{13}\text{R}^{14}$, $\text{-S(O)}_2\text{NR}^{13}\text{R}^{14}$,
 $\text{-NR}^{14}\text{C(O)NR}^{13}\text{R}^{14}$ or $\text{-NR}^{14}\text{C(NR}^{14}\text{)NR}^{13}\text{R}^{14}$, wherein R^{13} and R^{14} are as defined above, or
30 (ii) $(\text{C}_{3-12})\text{cycloalkyl}(\text{C}_{0-6})\text{alkyl}$, hetero $(\text{C}_{3-12})\text{cycloalkyl}(\text{C}_{0-6})\text{alkyl}$, $(\text{C}_{6-12})\text{aryl}(\text{C}_{0-6})\text{alkyl}$,
diphenyl $(\text{C}_{0-6})\text{alkyl}$, hetero $(\text{C}_{5-12})\text{aryl}(\text{C}_{0-6})\text{alkyl}$, dihetero $(\text{C}_{5-6})\text{aryl}(\text{C}_{0-6})\text{alkyl}$,
 $(\text{C}_{9-12})\text{polycycloaryl}(\text{C}_{0-6})\text{alkyl}$ or hetero $(\text{C}_{8-12})\text{polycycloaryl}(\text{C}_{0-6})\text{alkyl}$ optionally substituted with

-R¹⁵, -X⁷OR¹⁵, -X⁷SR¹⁵, -S(O)R¹⁵, -S(O)₂R¹⁵, -C(O)R¹⁵, -C(O)OR¹⁵, -X⁷NR¹⁵R¹⁶,
 -X⁷NR¹⁶C(O)OR¹⁵, -C(O)NR¹⁵R¹⁶, -S(O)₂NR¹⁵R¹⁶, -NR¹⁶C(O)NR¹⁵R¹⁶ or
 -NR¹⁶C(NR¹⁶)NR¹⁵R¹⁶, wherein X⁷, R¹⁵ and R¹⁶ are as defined above; wherein any 1 to 3
 annular atoms of any aromatic ring with available valences comprising R¹ optionally

5 independently are substituted with halo, nitro, cyano, (C₁₋₆)alkyl, halo-substituted(C₁₋₆)alkyl,
 -OR¹⁷, -C(O)R¹⁷, -C(O)OR¹⁷, -C(O)NR¹⁷R¹⁷, -S(O)₂NR¹⁷R¹⁷, -X⁷NR¹⁷R¹⁷,
 -X⁷NR¹⁷C(O)OR¹⁷, -X⁷NR¹⁷C(O)NR¹⁷R¹⁷ or -X⁷NR¹⁷C(NR¹⁷)NR¹⁷R¹⁷, wherein X⁷ and R¹⁷
 are as defined above;

R² is hydrogen or (C₁₋₆)alkyl;

10 R³ is phenyl(C₂₋₃)alkyl, hetero(C₅₋₆)aryl(C₂₋₃)alkyl, (C₅₋₆)cycloalkyl(C₂₋₃)alkyl or
 hetero(C₅₋₆)cycloalkyl(C₂₋₃)alkyl, wherein any 1 to 3 annular atoms of any aromatic ring with
 available valences comprising R³ optionally independently are substituted with halo, nitro, cyano,
 (C₁₋₆)alkyl, halo-substituted(C₁₋₆)alkyl, -OR¹⁷, -C(O)R¹⁷, -C(O)OR¹⁷, -C(O)NR¹⁷R¹⁷,
 -S(O)₂NR¹⁷R¹⁷, -X⁷NR¹⁷R¹⁷, -X⁷NR¹⁷C(O)OR¹⁷, -X⁷NR¹⁷C(O)NR¹⁷R¹⁷ or
 -X⁷NR¹⁷C(NR¹⁷)NR¹⁷R¹⁷, wherein X⁷ and R¹⁷ are as defined above, and R⁴ is hydrogen or R³
 and R⁴ are both methyl, ethyl or propyl or together with the carbon atom to which both R³ and
 R⁴ are attached form cyclopropylene, cyclobutylene or cyclopentylene;

R⁵ is hydrogen and R⁶ is hydroxy or R⁵ and R⁶ together form oxo;

R⁷ is halo, nitro, -R²⁰, -OR²⁰, -C(O)R²⁰, -C(O)OR²⁰, -S(O)₂NR²⁰R²¹, -C(O)NR²⁰R²¹ or

20 -C(O)NR²²CHR²³C(O)OR²⁰ and bonded to any annular carbon atom with a free valence
 comprising A, wherein:

R²⁰ is hydrogen or R¹⁸, wherein R¹⁸ is as defined above;

R²¹ is hydrogen or (C₁₋₆)alkyl;

R²² is hydrogen, (C₁₋₆)alkyl or together with R²³ forms trimethylene or

25 phenylene-1,2-dimethylene, optionally substituted with hydroxy or oxo; and

R²³ is as defined above or is (i) (C₁₋₆)alkyl or halo-substituted(C₁₋₆)alkyl
 optionally substituted with -OR¹³, -SR¹³, -S(O)R¹³, -S(O)₂R¹³, -C(O)R¹³, -C(O)OR¹³,
 -NR¹³R¹⁴, -NR¹⁴C(O)OR¹³, -C(O)NR¹³R¹⁴, -S(O)₂NR¹³R¹⁴, -NR¹⁴C(O)NR¹³R¹⁴ or
 -NR¹⁴C(NR¹⁴)NR¹³R¹⁴, wherein R¹³ and R¹⁴ are as defined above, or

30 (ii) (C₃₋₁₀)cycloalkyl(C₀₋₃)alkyl, hetero(C₃₋₁₀)cycloalkyl(C₀₋₃)alkyl, (C₆₋₁₂)aryl(C₀₋₃)alkyl,
 hetero(C₅₋₁₂)aryl(C₀₋₃)alkyl, (C₉₋₁₂)polycycloaryl(C₀₋₃)alkyl or
 hetero(C₈₋₁₂)polycycloaryl(C₀₋₃)alkyl optionally substituted with -R¹⁵, -X⁷OR¹⁵, -X⁷SR¹⁵,

-S(O)R¹⁵, -S(O)₂R¹⁵, -C(O)R¹⁵, -C(O)OR¹⁵, -X⁷NR¹⁵R¹⁶, -X⁷NR¹⁶C(O)OR¹⁵,
 -C(O)NR¹⁵R¹⁶, -S(O)₂NR¹⁵R¹⁶, -NR¹⁶C(O)NR¹⁵R¹⁶ or -NR¹⁶C(NR¹⁶)NR¹⁵R¹⁶,
 wherein X⁷, R¹⁵ and R¹⁶ are as defined above; wherein any 1 to 3 annular atoms of any
 aromatic ring with available valences comprising R²⁰ and/or R²¹ optionally independently
 5 are substituted with halo, nitro, cyano, (C₁₋₆)alkyl, halo-substituted(C₁₋₆)alkyl, -OR¹⁷,
 -C(O)R¹⁷, -C(O)OR¹⁷, -C(O)NR¹⁷R¹⁷, -S(O)₂NR¹⁷R¹⁷, -X⁷NR¹⁷R¹⁷,
 -X⁷NR¹⁷C(O)OR¹⁷, -X⁷NR¹⁷C(O)NR¹⁷R¹⁷ or -X⁷NR¹⁷C(NR¹⁷)NR¹⁷R¹⁷, wherein X⁷
 and R¹⁷ are as defined above; and
 R⁸ is hydrogen, halo, hydroxy, formyl, carboxy, carbamoyl, sulfamoyl or (C₁₋₆)alkyl and
 10 bonded to any annular carbon atom with a free valence comprising A; and the N-oxide
 derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of
 isomers; and the pharmaceutically acceptable salts thereof.

DETAILED DESCRIPTION OF THE INVENTION

Definitions:

15 Unless otherwise stated, the following terms used in the specification and claims are defined for the purposes of this Application and have the meanings given this Section:

“Alicyclic” means a moiety characterized by arrangement of the carbon atoms in closed non-aromatic ring structures having properties resembling those of aliphatics and may be saturated or partially unsaturated with two or more double or triple bonds.

20 “Aliphatic” means a moiety characterized by straight or branched chain arrangement of the constituent carbon atoms and may be saturated or partially unsaturated with two or more double or triple bonds.

“Alkenyl” means alkyl, as defined in this Application, provided that the radical is comprised of at least one double bond. Hence, optionally substituted (C₂₋₆)alkenyl as used in
 25 this Application to define R³² includes 2-bromovinyl (-CH₂CHBr), buta-1,3-dienyl (-CHCH-CH₂CH₂), 2-chloro-1-methylpropenyl (-C(CH₃)CCl-CH₃), 2-chlorovinyl (-CHCHCl), 4-isopropenyl (-C(CH₃)CH₂), 1-methylpropenyl (-C(CH₃)CH-CH₃), 2-methylpropenyl (-CHC(CH₃)₂), 2-nitrovinyl (-CHCHNO₂), propenyl (-CHCH-CH₃),

2-trifluoromethylvinyl (-CHCH-CF₃), trifluorovinyl (-CFCF₂), vinyl (-CHCH₂), and the like).

“Alkoxy” means the radical -OR, wherein R is alkyl as defined in this Application, having the number of carbon atoms indicated (e.g., (C₁₋₄)alkoxy includes the radicals methoxy, ethoxy, propoxy, isopropoxy, butoxy, *sec*-butoxy, isobutoxy, *tert*-butoxy, vinyloxy, allyloxy,

5 1-propenyl, isopropenyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-methylallyl, ethynyl, 1-propynyl, 2-propynyl, and the like).

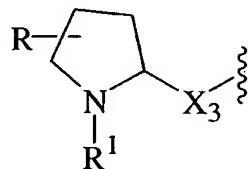
“Alkyl” represented by itself means a straight or branched, saturated or unsaturated, aliphatic radical having the number of carbon atoms indicated (e.g. (C₁₋₆)alkyl includes methyl, ethyl, propyl, isopropyl, butyl, *sec*-butyl, isobutyl, *tert*-butyl, vinyl, allyl, 1-propenyl, isopropenyl,

10 1-butyl, 2-butyl, 3-butyl, 2-methylallyl, ethynyl, 1-propynyl, 2-propynyl, and the like).

Alkyl represented along with another radical (e.g. as in arylalkyl) means a straight or branched, saturated or unsaturated aliphatic divalent radical having the number of atoms indicated or when no atoms are indicated means a bond (e.g. (C₆₋₁₂)aryl(C₀₋₆)alkyl includes phenyl, benzyl, phenethyl, 1-phenylethyl 3-phenylpropyl, and the like).

15 “Alkylene”, unless indicated otherwise, means a straight or branched, saturated or unsaturated, aliphatic, divalent radical having the number of carbon atoms indicated (e.g. (C₁₋₆)alkylene includes methylene (-CH₂-), ethylene (-CH₂CH₂-), trimethylene (-CH₂CH₂CH₂-), 2-methyltrimethylene (-CH₂CH(CH₃)CH₂-), tetramethylene (-CH₂CH₂CH₂CH₂-), 2-butenylene (-CH₂CH=CHCH₂-), 2-methyltetramethylene (-CH₂CH(CH₃)CH₂CH₂-), pentamethylene

20 (-CH₂CH₂CH₂CH₂CH₂-) and the like). For example, a group of Formula (a), wherein R¹¹ is hydrogen and R¹² taken together with R⁹ forms optionally substituted trimethylene is depicted by the following illustration:



in which R is an optional hydroxy or oxo group and X³ and R¹ are as defined in the Summary of
25 the Invention for Formulae I and II.

“Alkylidene” means a straight or branched saturated or unsaturated, aliphatic, divalent radical having the number of carbon atoms indicated (e.g. (C₁₋₆)alkylidene includes methylene (CH₂), ethylidene (CHCH₃), isopropylidene (C(CH₃)₂), propylidene (CHCH₂CH₃),